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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PATTON BOGGS LLP
8484 WESTPARK DRIVE
SUITE 900
MCLEAN, VA 22102

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,710	GRAHAM ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,77-100,102 and 104-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44, 77-100, 102, and 104-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An after final amendment was received and entered on 7/25/07.

Claims 101, 103, and 114-141 were canceled.

Claims 44, 77-100, 102, and 104-113 remain pending and are under consideration.

Finality of the previous Office Action is withdrawn in favor of this Action which is NON-FINAL due to new grounds of rejection not necessitated by amendment.

Claim Objections

Claim 89 is objected to in view of its recitation of "a monocotyledonous plant of a dicotyledonous plant. The word --or-- should be substituted for "of".

Third Party Submissions

Third-party submissions were filed under 37 CFR 1.99 on 2/23/07 and 3/6/07 in the published application.

To ensure that a third-party submission does not amount to a protest or pre-grant opposition, 37 CFR 1.99 does not permit the third party to have the right to insist that the examiner consider any of the patents or publications submitted. Furthermore, if the submission or part of the submission is not in compliance with 37 CFR 1.99, that noncompliant submission or part thereof will not be entered in the application file. Therefore, unless the examiner clearly cites a patent or publication on form PTO-892, Notice of References Cited and such reference is used in a rejection or its relevance is

actually discussed during prosecution, consideration by the examiner of any patent or publication submitted in a third-party submission cannot be presumed.

If the applicant wants to ensure that the information in a third-party submission is considered by the examiner, the applicant should submit the information in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98. An individual who has a duty to disclose under 37 CFR 1.56 should also submit any material information contained in a third-party submission to the Office in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98 to ensure such material information is properly disclosed to the examiner.

Applicant asserted in the response filed after final rejection on 7/12/07 and 7/25/07 that the third party submissions were improper under 37 CFR 1.99 because they were untimely, and that they should be removed from the file. This is unpersuasive because MPEP 1134.01 indicates that any submission not filed within the time period specified in 37 CFR 1.99(e) may be permitted when the patents or publications could not have been submitted to the Office earlier (e.g., an amendment submitted in the application after publication changes the scope of the claims to an extent that could not reasonably have been anticipated by a person reviewing the published application during the period specified in 37 CFR 1.99(e). In this case, one could not have reasonably anticipated amendments to the claims such as the requirement for an intron. Accordingly, the submissions are allowed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 100 and 104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 100 is indefinite because it is not clear how, and to what extent, the region of the transcript should correspond to 5'- or 3'-untranslated sequence of the target gene. The issue here is the indeterminate breadth of "correspond". One of skill in the art cannot know the metes and bounds of the genus of sequences deemed to "correspond to the target because the nature of the correspondence is not disclosed. The rejection could be overcome by rewriting the portion of the claim in question as "the region of the transcript is a 5'- or 3'-untranslated sequence."

Claim 104 is indefinite because it recites "the nucleic acid molecules" without proper antecedent basis. Substitution of "molecule" for molecules" is suggested. See e.g. claim 105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44, 85-87, 90, 91, 93, 100, 102, 104-106, 110, and 111, are rejected under 35 U.S.C. 102(b) as being anticipated by Haselbeck et al (Biochem. 32(33): 8575-8581, 1993).

Haselbeck taught Xenopus $tRNA^{Tyr}$ molecules comprising introns, and Xenopus oocytes comprising them. See abstract and Fig. 1 on page 8576. The $tRNA^{Tyr}$ molecules comprises several sequences of at least 20 nucleotides that are identical to those in a $tRNA^{Tyr}$ transcript (i.e. a $tRNA^{Tyr}$). The $tRNA^{Tyr}$ also contains several sequences that have partial complementarity to the first sequence, i.e. any sequence that forms the 3' portion of a stem structure wherein the 5' portion of the stem structure consists of part of the recited first sequence of 20 nucleotides. Finally, the $tRNA^{Tyr}$ molecules comprise introns in the anticodon loop. See Figs. 1 and 3 on pages 8576 and 8577.

Claims 85 and 87 are included in the rejection because a the status of the target gene as a transgene or an endogenous gene has no effect on the structure of the claimed isolated nucleic acid.

Claim 86 is included because tRNA genes are a considered to be a multigene family.

Claim 100 is included because the entire sequence of $tRNA^{Tyr}$ is untranslated.

Regarding claim 102, the stuffer fragment can be considered to be the sequence of the 2 right-most introns in Fig. 1, or any portion of sequence between the first 20 nucleotides of the tRNA and the last 7 nucleotides of the tRNA.

Thus Haselbeck anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44, 77, 80-87, 90, 91, 97-99, 102, 104-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of Kool (US 5,514,546), and Buchman et al (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired nucleotide loop structure (see e.g. Fig. 1, and page 15, lines 9-16). The target gene may be a viral gene. Disclosed viruses include human immunodeficiency virus, Yellow Fever virus (a single strand (+) RNA virus), and Herpes simplex virus (a double stranded DNA virus. See paragraph bridging pages 10 and 11. The target may be a member of a multi-gene family such as ras. See page 12, line 10. The oligonucleotide may be in a pharmaceutically acceptable carrier. See claim 18. Absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to vary the length of the unpaired loop sequence of the self-

stabilizing RNA of Agrawal in order to optimize hybridization of the complementary section of the oligonucleotides, thereby providing increased stability against nucleolytic attack.

Agrawal did not teach oligonucleotides comprising an intron.

Kool taught delivery of stem-loop oligonucleotides by expression vector or by direct application of the oligonucleotides. See abstract; Fig. 1; column 3, lines 16-19 and lines 58-62; column 4, lines 6-17; and column 14, lines 39-. Kool also disclosed antisense inhibition by targeting coding regions. See column 7, lines 43-46. Kool also disclosed delivery of expression vectors by viral- or liposome-mediated transfection. See column 15, lines 36-45; column 16, lines 43-47; paragraph bridging columns 24 and 25; and column 29, lines 32 and 33.

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the oligonucleotides of Agrawal by use of the expression vector of Kool. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Thus the delivery techniques of Kool, i.e. direct application of oligonucleotides, and transfection of oligonucleotide expression vectors, are considered to be exchangeable equivalents. Alternatively, the method of delivering the oligonucleotides can be viewed as a matter of design choice. Moreover, one would have been motivated to use the expression vector of Kool in order to obtain continuous

synthesis and action of oligonucleotides for the amount of time that the vector was present in the cell. Generally, expression vectors can be made with selectable markers that allow their maintenance in a cell for a longer time than the expected lifetime of an oligonucleotide. Thus one could reasonably expect to obtain antisense inhibition for a longer period of time with the expression vector of Kool.

It would have been similarly obvious to target coding regions of target genes, and to deliver the vectors by viral or liposomal means as suggested by Kool.

However, the combined references of Agrawal and Kool do not teach an RNA construct comprising an intron.

Buchman taught that the inclusion of an intron in an expression construct could stimulate transcription of the expressed transcript by 400-fold. See abstract.

It would have been obvious to include an intron in the expression vector of Kool in order to obtain the benefit of increased expression disclosed by Buchman. The resulting transcripts would contain, prior to processing, an intron.

Thus the invention as a whole was prima facie obvious.

Claims 44, 78, 79, 88, 89, and 112, and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of Day et al (Proc. Nat Acad. Sci. USA 88: 6721-6725, 1991), and Buchman et al (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is

self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired loop structure (see e.g. Fig. 1, and page 15, lines 9-16).

Agrawal did not teach RNA molecules directed against a plant virus, nor an expression construct encoding the RNA molecules.

Day taught that transgenic plants comprising an expression construct encoding antisense RNA directed against a Gemini virus gene were resistant to the virus. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Day by designing an expression construct encoding a self-stabilizing RNA molecule as taught by Agrawal. One would have been motivated to do so in order to increase the stability of the antisense RNA, thereby providing a reasonable expectation of improving viral resistance.

Buchman taught that the inclusion of an intron in an expression construct could stimulate transcription of the expressed by 400-fold. See abstract,.

It would have been obvious to include an intron in the expression construct of Day in order to obtain the benefit of increased expression as taught by Buchman. The resulting transcripts would contain, prior to processing, an intron.

Thus the invention as a whole was prima facie obvious.

Claims 44, 88, 89, 99, 100, 112, and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of Shewmaker et al (US Patent 5,107,065) and Buchman et al (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired loop structure (see e.g. Fig. 1, and page 15, lines 9-16).

Agrawal did not specifically teach an RNA with sequence identical to a region of a transcript in a plant cell, but noted that antisense regulation of gene expression in plant cells had been described, by Shewmaker, incorporating the teachings of Shewmaker by reference. Agrawal did not specify that the targeted region of the transcript was in the coding region or the 5'- or 3'-untranslated regions of the target. Agrawal did not teach an expression construct encoding the RNA molecules.

Shewmaker taught antisense regulation of gene expression in monocot or dicot plant cells by integrating into the genome of the plant cell a construct comprising in the 5'-3' direction of transcription a promoter functional in said plant cell, a dsDNA sequence wherein the transcribed strand of said dsDNA is complementary to RNA indigenous to said cell, whereby said complementary strand is transcribed and binds to said RNA

indigenous to said cell, thereby inhibiting expression of said gene indigenous to said plant cell. See abstract, column 4, lines 1-3, and claims 6 and 7. The transcribed RNA can comprise sequence from either the 5' or 3' untranslated region. See e.g. claims 3 and 4. Alternatively the transcribed RNA can comprise sequence from all or part of the coding region. See column 2, lines 33-50.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Shewmaker by designing an expression construct encoding a self-stabilizing RNA molecule as taught by Agrawal. One would have been motivated to do so in order to increase the stability of the antisense RNA, thereby providing a reasonable expectation of improving antisense performance.

Buchman taught that the inclusion of an intron in an expression construct could stimulate transcription of the expressed by 400-fold. See abstract,.

It would have been obvious to include an intron in the expression construct of Shewmaker in order to obtain the benefit of increased expression as taught by Buchman. The resulting transcripts would contain, prior to processing, an intron.

Thus the invention as a whole was prima facie obvious.

Claims 44, 90, 92, and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of McGarry et al (Proc Nat. Acad. Sci. USA 83:399-403, 1986) and Buchman et al (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired loop structure (see e.g. Fig. 1, and page 15, lines 9-16).

Agrawal did not teach RNA molecules comprising an intron, or RNA molecules directed against an RNA in a cell of an invertebrate animal or insect.

McGarry taught methods of inhibiting gene expression by expression of antisense RNA in cultured Drosophila cells.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of McGarry by designing an expression construct encoding a self-stabilizing RNA molecule as taught by Agrawal. One would have been motivated to do so in order to increase the stability of the antisense RNA, thereby providing a reasonable expectation of improving antisense performance.

Buchman taught that the inclusion of an intron in an expression construct could stimulate transcription of the expressed by 400-fold. See abstract,.

It would have been obvious to include an intron in the expression vector of McGarry in order to obtain the benefit of increased expression as taught by Buchman. The resulting transcripts would contain, prior to processing, an intron.

Thus the invention as a whole was prima facie obvious.

Claims 93 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal, Kool, and Buchman as applied to claims 44, 77, 80-87, 90, 91, 97-99, 102, 104-113 above, and further in view of Barabino et al (Mech. Dev. 63: 133-143, 1997).

Agrawal, Kool, and Buchman rendered obvious an isolated nucleic acid molecule comprising a first RNA sequence of greater than 20 consecutive nucleotides that is identical to a sequence of a transcript of a target gene in a eukaryotic cell, and a second RNA sequence complementary to the first RNA sequence, wherein the first and second sequences are in the same nucleic acid strand, are separated by a stuffer sequence of nucleotides, and wherein the nucleic acid molecule comprises an intron.

The combined references did not teach RNA molecules directed against an RNA in a cell of an aquatic animal.

Barabino taught methods of suppressing Alx gene expression in zebrafish embryos by administration of antisense oligonucleotides. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Barabino by designing and using expression vectors encoding self-stabilizing antisense RNA molecules as taught by Agrawal, Kool, and Buchman. One would have been motivated to do so in order to increase antisense performance.

Thus the invention as a whole was prima facie obvious.

Claims 96 is rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal, Kool, and Buchman as applied to claims 44, 77, 80-87, 90, 91, 97-99, 102, 104-113 above, and further in view of Swamynathan et al (J. Virol. 71(4): 2873-2880, 1997).

Agrawal, Kool, and Buchman rendered obvious an isolated nucleic acid molecule comprising a first RNA sequence of greater than 20 consecutive nucleotides that is identical to a sequence of a transcript of a target gene in a eukaryotic cell, and a second RNA sequence complementary to the first RNA sequence, wherein the first and second sequences are in the same nucleic acid strand, are separated by a stuffer sequence of nucleotides, and wherein the nucleic acid molecule comprises an intron.

The combined references did not teach RNA molecules directed against an RNA in a cell of an avian animal.

Swamynathan taught a method of inhibiting expression of chicken YB-2 in avian fibroblasts by administration of antisense RNA directed against the ama-1 gene. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Swamynathan by designing and using self-stabilizing antisense RNA molecules as taught by Agrawal, Kool, and Buchman. One would have been motivated to do so in order to increase antisense performance.

Thus the invention as a whole was prima facie obvious.

Claims 44, 77, 80-82, 85-95, 97-99, and 104-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire (US 6,506,559) in view of any one of Szyf et al (US Patent 5,578,716), Zamecnik (WO 97/11170), or Urdea (US Patent 5,631,148).

Fire disclosed and claimed methods for regulating gene expression in cells, including plant and animal cells, comprising introducing into a cell a double stranded RNA comprising a sequence complementary to a portion of the target gene and a sequence identical to a portion of the target gene. At column 4, lines 41-46 Fire et al. teach that the dsRNA can be formed from 1 or 2 strands. At columns 7-9, Fire et al. teach that the RNA can be synthesized in vivo or in vitro, can be expressed from a vector and can have a length of greater than 25 nucleotides (see col. 7, lines 53-co1.8, lines 12). The target gene can be a transgene (column 6, lines 44-49), a multigene family member (column 1, lines 13-16), a dicot (bean) or monocot (corn) plant gene (column 8, lines 14, 15, 20 and 21), a vertebrate, invertebrate, fish, mammal, human, or insect gene (column 8, lines 35-51).

Fire also exemplifies a double stranded RNA comprising an intron. See Table 1 at column 23/24, "unc22C", and column 23 at line 60, which disclose that unc22C is a dsRNA comprising a 43 nucleotide intron that was injected into C. elegans.

Thus Fire taught single strand RNAs comprising a first sequence of greater than 20 nucleotides identical to a target sequence in the transcript of a target gene of a eukaryotic cell, a second sequence complementary to the first, and an intron.

Fire was silent in regard to a stuffer fragment consisting of a sequence of nucleotides.

However, Fire taught that double stranded RNA may be formed from a single self-complementary nucleic acid (forming hairpin dsDNA).

Szyf taught that the hairpin structures disclosed therein "will presumably have loops of 4 or more nucleotides resulting from non-base- paired nucleotides" (US patent 5,578,716, col. 7, lines 29-33).

Similarly, Zamecnik taught that the sense and antisense regions of the disclosed duplexes may be joined by a loop of 3-6 bases (see p. 8, lines 4-5).

Finally, Urdea taught that a sequence of 1-100 nucleotides may intervene between the substrate binding region and the competitive binding sequence of the disclosed ribozyme oligonucleotides (see col. 7, lines 10-28).

Accordingly, it would have been obvious at the time the instant invention was made to modify the Fire patent to utilize a stuffer nucleotide fragment between the sense and antisense coding regions in a self-complementary nucleic acid in order to facilitate duplex formation as taught by the Szyf et al., Zamecnik or Urdea. It would have been similarly obvious to target a region of any target gene wherein the region encompasses an intron, because Fire exemplified such.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635